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(54) Title: METHOD FOR ADMINISTERING HEMOGLOBIN

(57) Abstract

A method for administering hemoglobin to a patient in need thereof comprising a pharmacokinetics administration wherein a hemoglobin containing composition is first administered as a loading dose calculated upon the concentration of hemoglobin desired in said patient and said patient's apparent volume of distribution; and thereafter administered as a maintenance dose calculated to maintain a steady-state hemoglobin level in the patient. The maintenance dose can be administered as a continuous infusion or as single doses. The method is useful for the administration of all blood components and all blood sources and can be performed in emergency, trauma, presurgical, surgical or post-operative situations wherever it is desirable to replace, control, elevate or maintain a blood component, especially hemoglobin level in a patient.

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METHOD FOR ADMINISTERING HEMOGLOBIN

Background of the Invention

The present invention is directed toward a novel approach for administering hemoglobin to patients in need of replacing, maintaining or elevating their hemoglobin levels. The traditional techniques for administering blood components has been to give a continuous infusion. Typically, a blood transfusion for elective or non-emergence indications involves administering one to two units of whole blood or packed red cells to a patient over a four hour period or longer. The subject method utilizes pharmacokinetic principals to first administer a loading dose and then a continuous small dose infusion to maintain a desired hemoglobin level in the blood stream. This method is particularly useful in the infusion of blood substitutes where it is desirable to maintain a relatively low level of unnatural blood in the patient's blood stream to avoid toxicity or rejection while providing the necessary benefits of oxygen transport.

There exists a critical need in the medical industry to find alternative blood sources due to lack of sufficient blood donors and the potential contamination of available blood supplies with various transfusable diseases. One impediment to developing alternative blood substitutes is the very complicated role blood plays in the body and the body's rejection of foreign blood components. The biotechnology industry has been attempting to develop an alternative blood source from porcine, bovine, outdated human blood and recombinant blood but all have encountered difficulties when administering them to patients. Difficulties include such problems as kidney and liver function abnormalities, gastric distress and blood pressure fluctuations.

The present invention attempts to solve these problems by introducing a novel method for administration of blood components, especially blood substitutes. It has now been discovered that by employing pharmacokinetic principals instead of large scale transfusions one can minimize the amount of foreign bodies introduced into the patient but still replace, maintain or elevate a desired hemoglobin level to provide necessary oxygen transport in the patient.

Summary of the Invention

In one aspect, the present invention is a method for administering hemoglobin to a patient in need thereof comprising the administration of a loading dose of a hemoglobin containing composition based upon the concentration of hemoglobin desired in a patient and the patient's apparent volume of distribution; and thereafter the administration of a maintenance dose of the hemoglobin containing composition calculated to maintain a steady-state hemoglobin level in the patient. The maintenance dose can be administered as a continuous infusion or as single doses.

The hemoglobin containing composition can be a blood substitute comprising

hemoglobin suspended in a pharmaceutically acceptable vehicle for administration such as modified regular donated or transfused blood, packed red blood cells, reconstituted human or other animal species blood synthesized for administration to the patient, a recombinant or other blood substitute. A pharmaceutically acceptable vehicle for administration is any liquid or diluent suitable for admixing hemoglobin which does not interfere with its oxygen carrying role or have an adverse effect on the patient. Such vehicles are well known in the art and include for example, normal saline or lactated Ringer's. Preferred blood substitutes are crosslinked hemoglobin essentially free of 64,000 molecular weight or less hemoglobin components (i.e., tetramer free).

Detailed Description of the Invention

The present invention discloses the pharmacokinetic dosing of blood components, preferably hemoglobin to a patient in need of having their hemoglobin level replaced due to blood lose, maintained or modified for a therapeutic purpose, elevated or otherwise controlled. A patient can be any mammal having a hemoglobin oxygen transportation mechanism for sustaining cell function. This administration procedure should be effective for all blood components such as white blood cells, red blood cells, platelets, plasma, Factor VIII, IX and XI.

Particularly useful in the subject method is the administration of blood substitutes such as blood or blood components not derived from the patient that is receiving such blood or blood component. The present method is advantageously used for blood substitutes because it allows the practitioner to minimize the total exposure of the transfused blood to the patient over time, thus avoiding any dose related toxicity problems from the particular blood source utilized. Typical blood substitutes are porcine derived blood components available from DNX, Princeton, NJ; recombinant derived blood components available from Somatogen, Inc., Boulder, CO (US Patent 5,028,588); processed human blood such as by purifying and crosslinking outdated human blood available from Northfield Labs Inc., Evanston, IL (US Patents 4,826,811, 5,194,590 and 5,194,270); and Baxter, Northfield, IL (US Patents 5,128,452, 4,861,867 and 4,831,012); bovine derived blood substitutes available from Enzon, S. Plainfield, NJ, and Biopure, Boston, MA (US Patent 5,084,558); and oxygen carrying fluorocarbons available through Alliance Pharm. Corp., San Diego, CA.

The hemoglobin is generally administered to a patient in need of such hemoglobin in a pharmaceutically acceptable vehicle. A pharmaceutically acceptable vehicle for administration is any liquid or diluent suitable for admixing hemoglobin which does not interfere with its oxygen carrying role or have an adverse effect on the patient. Such vehicles are well known in the art and include for example, normal saline or lactated Ringer's.

With any of the mentioned blood substitutes the subject method provides the distinct advantage of minimizing the amount of blood substitute needed to replace the oxygen carrying capacity of the native hemoglobin lost from a patient. In another aspect, the subject method allows the practitioner to elevate or maintain oxygen carrying capacity of the blood stream by administering controlled minimal amounts of a blood substitute.

Preferably, large molecular weight hemoglobin substitutes (blood substitutes) are administered because these have been found to have fewer side effects or adverse reactions. High molecular weight, crosslinked hemoglobin are preferred because they result in the formation of high molecular weight oligomers of the hemoglobin tetramer which are extremely resistant to renal filtration and more stable to oxidation at physiological temperature than either unmodified hemoglobin or hemoglobin crosslinked to only the tetramer-dimer level.

Particularly preferred are the crosslinked, polymerized hemoglobin which are relatively free of tetramer or dimer components, i.e., having molecular weights greater than 64,000, but still possessing a P50 or oxygen affinity which is low enough to effectively transport oxygen and then release it to the cells of a living organism. Hemoglobin compositions having less than 10% tetramer or dimer components are preferred with less than 6% being particularly preferred and essentially tetramer free compositions being most preferred. Examples of such tetramer free blood substitutes are disclosed in US Patent 5,194,590 to Northfield Laboratories, Inc., Evanston, Il.

Other blood substitutes derived from various blood sources can also be filtered by molecular weight sieves or filters to eliminate essentially all tetramer and lower weight material to prepare this preferred material. Methods to prepare high molecular weight blood substitutes can include a step where the purified, cross-linked hemoglobin is size excluded to remove low molecular weight hemoglobin (less than 64,000). Typically, this size exclusion is by low pressure size exclusion chromatography.

In many cases, the blood substitutes have an oxygen affinity of the hemoglobin or P50 value which is low enough to effectively transport oxygen and then release it to the cells of a living organism more efficiently than native human hemoglobin. The P50 is the partial pressure of oxygen at which 50% of the available sites have bound oxygen. Thus, it has been discovered that a gram per gram replacement of hemoglobin is not necessary to maintain, elevate or replace the oxygen carrying capacity of native human hemoglobin. Mere volume replacement can be achieved with other known blood volume expanders and thereby the subject method minimizes the opportunity for the treated patient to adversely react to a large infusion of blood substitutes which may be foreign to the patient, such as from a different species or artificial sources including recombinant means.

Pharmacokinetic dosing is a well understood method of dosing patients for intravenous drugs but has not been employed for transfusing blood. Pharmacokinetic dosing relies on calculating a loading dose usually based on the patient's weight and then a corresponding continuous infusion rate or maintenance dose, for maintaining a particular dosage level in the patient. The determination for the dose to use for the loading dose will be based on dosing in grams of hemoglobin per body weight or volume of fluid (mls of the blood substitute as based upon its content of hemoglobin) needed.

Many basic texts on performing pharmacokinetic dosing exist such as Ansel, H.C. Introduction to Pharmaceutical Dosage Forms (3rd ed.), Philadelphia: Lea & Febiger (1981). Numerous methods, formulas, nomograms and computer programs are designed to simplify dosage regimen calculations and have been published in the medical literature although not for blood. The loading dose is dependent only on the desired concentration and apparent volume of distribution of the drug, in this case the concentration of hemoglobin in the patient's total blood volume. However, other factors such as state of the emergency or amount of overall blood loss that change volume of distributions are to be considered.

The continuous infusion rate or maintenance dosage regimen is to achieve a consistently desired concentration with a dose size and frequency that is practical without marked fluctuations in blood component, hemoglobin, concentrations. Consistency of concentrations is best maintained with continuous intravenous infusions or very frequent small doses. Particularly preferred with respect to the administration of a blood substitute is that the maintenance dose or continuous infusion is at a level to not produce toxicity and such that the concentration does not drop for long below the therapeutic range.

The maintenance dose is directed influenced by the clearance rate of the particular blood substitute employed and inversely related to changes in half life. These factors are known for the variously available blood substitutes and can be easily factored into any maintenance calculation formula. The pharmacokinetics method of dosing is particular favorable for blood substitutes because it is easy to monitor not only hemoglobin level in a patient but also to monitor the individual species of the blood substitute itself. Thus, pharmacokinetic models for the particular blood substitute are easily prepared for proper administration.

For example, if one desires a specific plasma hemoglobin concentration, one can calculate the amount (grams or milliliters) that are needed to raise the hemoglobin levels based on the patient's body weight. A loading dose given over a specified time to achieve these target concentrations. A continuous infusion is started immediately after the loading dose is given. The purpose of the loading dose is to be able to maintain steady-state plasma concentrations of hemoglobin. The duration of administration of the continuous infusion will be up to 24 hours, but may exceed this, if clinically indicated. Furthermore, this dosing may be done anywhere in

the preoperative period or during the operation itself. Small repeated bolus (or loading doses) may be necessary to maintain plasma hemoglobin levels, in the case of surgical blood loss, in excess of predicted amounts. The procedure above should not be limited to a particular type of surgery, but globally to the patient who is in need of a transfusion .

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What is Claimed:

1. A method for administering hemoglobin to a patient in need thereof comprising:

a) administering a loading dose of a hemoglobin containing composition based upon the concentration of hemoglobin desired in said patient and said patient's apparent volume of distribution; and thereafter

b) administering a maintenance dose of said hemoglobin containing composition calculated to maintain a steady-state hemoglobin level in said patient.

2. The method of Claim 1 wherein said maintenance dose is administered as a continuous infusion.

3. The method of Claim 1 wherein said hemoglobin containing composition is a blood substitute comprising hemoglobin suspended in a pharmaceutically acceptable vehicle for administration.

4. The method of Claim 1 wherein said maintenance dose is administered as frequent single doses.

5. The method of Claim 1 wherein said hemoglobin is a cross-linked blood substitute.

6. The method of Claim 1 wherein said hemoglobin is essentially free of tetramer or lower molecular weight hemoglobin.

7. A hemoglobin composition for use in treating a patient in need of hemoglobin where the hemoglobin composition is administered as a loading dose based upon the concentration of hemoglobin desired in the patient and the patient's apparent volume of distribution and thereafter administering a maintenance dose of the hemoglobin containing composition calculated to maintain a steady-state hemoglobin level in the patient.

INTERNATIONAL SEARCH REPORT

Inter[redacted]Application No
PCT/US 94/06030

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO,A,87 07832 (NORTHFIELD LABORATORIES,INC) 30 December 1987 see the whole document & US,A,5 194 590 (SEHGAL ET AL) cited in the application	7 1-6
Y	FILE SERVER STN KARLSRUHE,FILE MEDLINE ABSTRACT NO.86048841 & AM J VET RES, (1985 OCT) 46 (10) 2175-8 ENGELKING ET AL:'ENHANCED BILIARY BILIRUBIN EXCRETION AFTER HEPARIN-INDUCED ERYTHROCYTE MASS DEPLETION' see abstract	1-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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Date of the actual completion of the international search	Date of mailing of the international search report
27 September 1994	27. 10. 94

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FILE SERVER STN KARLSRUHE,FILE MEDLINE ABSTRACT NO.84102558 & AM J VET RES, (1983 DEC) 44 (12) 2271-6 DUNCAN ET AL:'REDUCTION OF THE RED BLOOD CELL MASS OF HORSES:TOXIC EFFECT OF HEPARIN ANTICOAGULANT THERAPY' see abstract ---	1-6
Y	FILE SERVER STN KARLSRUHE,FILE MEDLINE ABSTRACT NO.77139496 & FORTSCHR MED, (1977 APR 7) 95 (13) 858-66 KRIESSMANN ET AL:'FIBRINOLYTIC THERAPY IN DEEP VENOUS THROMBOSIS OF THE UPPER AND LOWER EXTREMITY' see abstract -----	1-6

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/ 06030

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-6 are directed to a method of treatment of the human/animal body the search ahs been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern Application No
PCT/US 94/06030

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8707832	30-12-87	US-A-	4826811	02-05-89
		DE-T-	3790322	15-09-88
		EP-A,B	0271542	22-06-88
		FR-A-	2600255	24-12-87
		GB-A,B	2200639	10-08-88
		JP-T-	1501471	25-05-89
		NL-A-	8720283	02-05-88
US-A-5194590	16-03-93	NONE		